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(71) Applicant *(for all designated States except MG, US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Sodertalje (SE).

(71) Applicant *(for MG only)*: ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BRADBURY, Robert, Hugh [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, MacClesfield, Cheshire SK10 4TG (GB). HENNEQUIN, Laurent, Francois, Andre [FR/FR]; AstraZeneca Pharma, Z.I. la Pompelle, BP 1050, F-51689 Reims (FR). BARLAAM, Bernard, Christophe [FR/FR]; AstraZeneca Pharma, Z. I. la Pompelle, BP 1050, F-51689 Reims Cedex 02 (FR).

(74) Agent: ASTRAZENECA; Global Intellectual Property, S-151 85 Sodertalje (SE).

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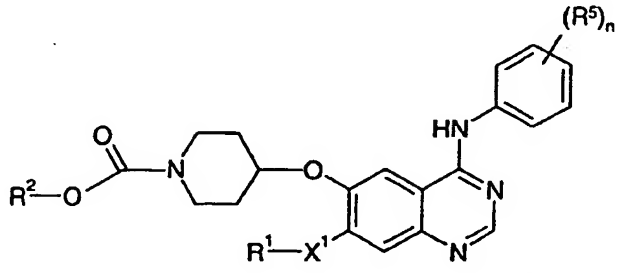
(54) Title: QUINAZOLINE DERIVATIVES




(I)

(57) Abstract: The invention concerns quinazoline derivatives of Formula (I): wherein each of $R^1$, $R^2$, $X^1$, $R^5$ and m have any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use as an antiproliferative agent in the prevention or treatment of tumours which are sensitive to inhibition of EGF and erbB receptor tyrosine kinases.

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# QUINAZOLINE DERIVATIVES

The invention concerns certain novel quinazoline derivatives, or pharmaceutically acceptable salts thereof, which possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body. The invention also concerns processes for the manufacture of said quinazoline derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

Many of the current treatment regimes for diseases resulting from the abnormal regulation of cellular proliferation such as psoriasis and cancer, utilise compounds that inhibit DNA synthesis and cellular proliferation. To date, compounds used in such treatments are generally toxic to cells however their enhanced effects on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to these cytotoxic anti-tumour agents are currently being developed, for example selective inhibitors of cell signalling pathways. These types of inhibitors are likely to have the potential to display an enhanced selectivity of action against tumour cells and so are likely to reduce the probability of the therapy possessing unwanted side effects.

Eukaryotic cells are continually responding to many diverse extracellular signals that enable communication between cells within an organism. These signals regulate a wide variety of physical responses in the cell including proliferation, differentiation, apoptosis and motility. The extracellular signals take the form of a diverse variety of soluble factors including growth factors as well as paracrine and endocrine factors. By binding to specific transmembrane receptors, these ligands integrate the extracellular signal to the intracellular signalling pathways, therefore transducing the signal across the plasma membrane and allowing the individual cell to respond to its extracellular signals. Many of these signal transduction processes utilise the reversible process of the phosphorylation of proteins that are involved in the promotion of these diverse cellular responses. The phosphorylation status of target proteins is regulated by specific kinases and phosphatases that are responsible for the regulation of about one third of all proteins encoded by the mammalian genome. As phosphorylation is such an important regulatory mechanism in the signal transduction process, it is therefore not surprising that aberrations in these intracellular pathways result in

abnormal cell growth and differentiation and so promote cellular transformation (reviewed in Cohen *et al*, Curr Opin Chem Biol, 1999, 3, 459-465).

It has been widely shown that a number of these tyrosine kinases are mutated to constitutively active forms and/or when over-expressed result in the transformation of a variety of human cells. These mutated and over-expressed forms of the kinase are present in a large proportion of human tumours (reviewed in Kolibaba *et al*, Biochimica et Biophysica Acta, 1997, 133, F217-F248). As tyrosine kinases play fundamental roles in the proliferation and differentiation of a variety of tissues, much focus has centred on these enzymes in the development of novel anti-cancer therapies. This family of enzymes is divided into two groups - receptor and non-receptor tyrosine kinases e.g. EGF Receptors and the SRC family respectively. From the results of a large number of studies including the Human Genome Project, about 90 tyrosine kinase have been identified in the human genome, of this 58 are of the receptor type and 32 are of the non-receptor type. These can be compartmentalised in to 20 receptor tyrosine kinase and 10 non-receptor tyrosine kinase sub-families (Robinson *et al*, Oncogene, 2000, 19, 5548-5557).

The receptor tyrosine kinases are of particular importance in the transmission of mitogenic signals that initiate cellular replication. These large glycoproteins, which span the plasma membrane of the cell possess an extracellular binding domain for their specific ligands (such as Epidermal Growth Factor (EGF) for the EGF Receptor). Binding of ligand results in the activation of the receptor's kinase enzymatic activity that is encoded by the intracellular portion of the receptor. This activity phosphorylates key tyrosine amino acids in target proteins, resulting in the transduction of proliferative signals across the plasma membrane of the cell.

It is known that the erbB family of receptor tyrosine kinases, which include EGFR, erbB2, erbB3 and erbB4, are frequently involved in driving the proliferation and survival of tumour cells (reviewed in Olayioye et al., EMBO J., 2000, 19, 3159). One mechanism in which this can be accomplished is by overexpression of the receptor at the protein level, generally as a result of gene amplification. This has been observed in many common human cancers (reviewed in Klapper et al., Adv. Cancer Res., 2000, 77, 25) such as breast cancer (Sainsbury et al., Brit. J. Cancer, 1988, 58, 458; Guerin et al., Oncogene Res., 1988, 3, 21; Slamon et al., Science, 1989, 244, 707; Klijn et al., Breast Cancer Res. Treat., 1994, 29, 73 and reviewed in Salomon et al., Crit. Rev. Oncol. Hematol., 1995, 19, 183), non-small cell lung cancers (NSCLCs) including adenocarcinomas (Cerny et al., Brit. J. Cancer, 1986, 54,

265; Reubi et al., Int. J. Cancer, 1990, 45, 269; Rusch et al., Cancer Research, 1993, 53, 2379; Brabender et al, Clin. Cancer Res., 2001, 7, 1850) as well as other cancers of the lung (Hendler et al., Cancer Cells, 1989, 7, 347; Ohsaki et al., Oncol. Rep., 2000, 7, 603), bladder cancer (Neal et al., Lancet, 1985, 366; Chow et al., Clin. Cancer Res., 2001, 7, 1957, Zhau et al., Mol Carcinog., 3, 254), oesophageal cancer (Mukaida et al., Cancer, 1991, 68, 142), gastrointestinal cancer such as colon, rectal or stomach cancer (Bolen et al., Oncogene Res., 1987, 1, 149; Kapitanovic et al., Gastroenterology, 2000, 112, 1103; Ross et al., Cancer Invest., 2001, 19, 554), cancer of the prostate (Visakorpi et al., Histochem. J., 1992, 24, 481; Kumar et al., 2000, 32, 73; Scher et al., J. Natl. Cancer Inst., 2000, 92, 1866), leukaemia (Konaka et al., Cell, 1984, 37, 1035, Martin-Subero et al., Cancer Genet Cytogenet., 2001, 127, 174), ovarian (Hellstrom et al., Cancer Res., 2001, 61, 2420), head and neck (Shiga *et al.*, Head Neck, 2000, 22, 599) or pancreatic cancer (Ovotny et al., Neoplasma, 2001, 48, 188). As more human tumour tissues are tested for expression of the erbB family of receptor tyrosine kinases it is expected that their widespread prevalence and importance will be further enhanced in the future.

As a consequence of the mis-regulation of one or more of these receptors, it is widely believed that many tumours become clinically more aggressive and so correlate with a poorer prognosis for the patient (Brabender et al, Clin. Cancer Res., 2001, 7, 1850; Ross et al, Cancer Investigation, 2001, 19, 554, Yu et al., Bioessays, 2000, 22.7, 673). In addition to these clinical findings, a wealth of pre-clinical information suggests that the erbB family of receptor tyrosine kinases are involved in cellular transformation. This includes the observations that many tumour cell lines overexpress one or more of the erbB receptors and that EGFR or erbB2 when transfected into non-tumour cells have the ability to transform these cells. This tumourigenic potential has been further verified as transgenic mice that overexpress erbB2 spontaneously develop tumours in the mammary gland. In addition to this, a number of pre-clinical studies have demonstrated that anti-proliferative effects can be induced by knocking out one or more erbB activities by small molecule inhibitors, dominant negatives or inhibitory antibodies (reviewed in Mendelsohn et al., Oncogene, 2000, 19, 6550). Thus it has been recognised that inhibitors of these receptor tyrosine kinases should be of value as a selective inhibitor of the proliferation of mammalian cancer cells (Yaish *et al.* Science, 1988, 242, 933, Kolibaba *et al*, Biochimica et Biophysica Acta, 1997, 133, F217-F248; Al-Obeidi *et al*, 2000, Oncogene, 19, 5690-5701; Mendelsohn *et al*, 2000, Oncogene, 19, 6550-6565). In addition to this pre-clinical data, findings using inhibitory antibodies against EGFR and erbB2

(c-225 and trastuzumab respectively) have proven to be beneficial in the clinic for the treatment of selected solid tumours (reviewed in Mendelsohn *et al*, 2000, Oncogene, 19, 6550-6565).

Amplification and/or activity of members of the erbB type receptor tyrosine kinases have been detected and so have been implicated to play a role in a number of non-malignant proliferative disorders such as psoriasis (Ben-Bassat, Curr. Pharm. Des., 2000, 6, 933; Elder et al., Science, 1989, 243, 811), benign prostatic hyperplasia (BPH) (Kumar et al., Int. Urol. Nephrol., 2000, 32,73), atherosclerosis and restenosis (Bokemeyer et al., Kidney Int., 2000, 58, 549). It is therefore expected that inhibitors of erbB type receptor tyrosine kinases will be useful in the treatment of these and other non-malignant disorders of excessive cellular proliferation.

European patent application EP 566 226 discloses certain 4-anilinoquinazolines that are receptor tyrosine kinase inhibitors.

International patent applications WO 96/33977, WO 96/33978, WO 96/33979, WO 96/33980, WO 96/33981, WO 97/30034, WO 97/38994 disclose that certain quinazoline derivatives which bear an anilino substituent at the 4-position and a substituent at the 6- and/or 7- position possess receptor tyrosine kinase inhibitory activity.

European patent application EP 837 063 discloses aryl substituted 4-aminoquinazoline derivatives carrying a moiety containing an aryl or heteroaryl group at the 6-or 7- position on the quinazoline ring. The compounds are stated to be useful for treating hyperproliferative disorders.

International patent applications WO 97/30035 and WO 98/13354 disclose certain 4-anilinoquinazolines substituted at the 7- position are vascular endothelial growth factor receptor tyrosine kinase inhibitors.

WO 00/55141 discloses 6,7-substituted 4-anilinoquinazoline compounds characterised in that the substituents at the 6-and/or 7-position carry an ester linked moiety (RO-CO).

WO 00/56720 discloses 6,7-dialkoxy-4-anilinoquinazoline compounds for the treatment of cancer or allergic reactions.

WO 02/41882 discloses 4-anilinoquinazoline compounds substituted at the 6- and/or 7- position by a substituted pyrrolidinyl-alkoxy or piperidinyl-alkoxy group.

WO 03/082290 discloses that certain 6,7-substituted 4-anilinoquinazoline compounds possess receptor tyrosine kinase inhibitory activity. A specific example of such a compound is

4-[(3-chloro-4-fluorophenyl)amino]-6-[1-(tert-butyloxycarbonyl)-piperidin-4-yl-oxy]-7-methoxy-quinazoline.

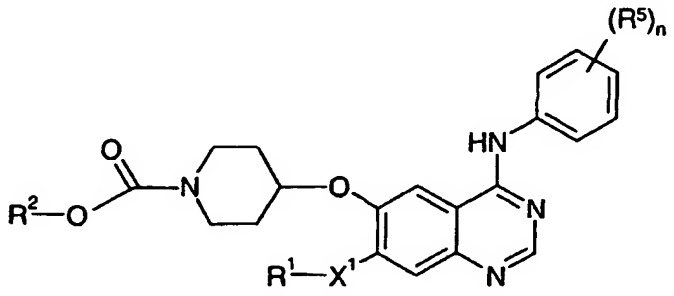
None of the above prior art discloses 4-(2,3-dihalogenoanilino)quinazoline or 4-(2,3,4-trihalogenoanilino)quinazoline compounds.

Copending International Patent Application No. PCT/GB03/01306 describes that certain 4-(2,3-dihalogenoanilino)quinazoline derivatives that possess potent anti-tumour activity, and in particular are selective against EGFR. A specific example of such a compound is 6-(1-acetylpiperidin-4-yloxy)-4-(3-chloro-2-fluoro anilino)-7-methoxy-quinazoline.

The applicants have surprisingly found however that modification of a side chain and, optionally, adding a further substituent to the aniline group produces a select group of compounds with enhanced activity in that the compounds have a good erbB2 kinase inhibitory effect in addition to a EGF inhibitory effect, making them of particular clinical application in the treatment of tumours where both these kinases are implicated.

Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of two of the erbB family of receptor tyrosine kinases that are involved in the signal transduction steps which lead to the proliferation of tumour cells. In particular, it is believed that the compounds of the present invention provide an anti-tumour effect by way of inhibition of EGFR and/or erbB2 receptor tyrosine kinases.

According to a first aspect of the invention there is provided a quinazoline derivative of the Formula I:




I

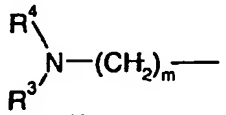
wherein n is 0, 1, 2 or 3,

each $R^5$ is independently selected from halogeno, cyano, nitro, hydroxy, amino, carboxy, sulfamoyl, trifluoromethyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylsulfamoyl, and N,N-di-[(1-6C)alkyl]sulfamoyl, $C(O)NR^6R^7$ where $R^6$ and $R^7$ are independently selected from hydrogen, optionally substituted (1-6C)alkyl, optionally substituted (3-8C)cycloalkyl or optionally substituted aryl, or $R^6$ and $R^7$ together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring which may contain additional heteroatoms;

$X^1$ is a direct bond or O;

$R^1$ is selected from hydrogen and (1-6C)alkyl, wherein the (1-6C)alkyl group is optionally substituted by one or more substituents, which may be the same or different, selected from hydroxy and halogeno, and/or a substituent selected from amino, nitro, carboxy, cyano, halogeno, (1-6C)alkoxy, hydroxy(1-6C)alkoxy, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, N-(1-6C)alkylcarbamoyl, N,N di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (1-6C)alkoxycarbonyl, sulfamoyl, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino;

$R^2$ is (1-6C)alkyl, (2-6C)alkenyl or (2-6C)alkynyl, any of which may be optionally substituted by fluoro, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, or a group of sub-formula (i)



(i)

wherein m is 0, 1, 2 or 3;

$R^3$ and $R^4$ are independently selected from hydrogen or (1-6C)alkyl, or $R^3$ and $R^4$ together with the nitrogen atom to which they are attached form a saturated 5 or 6 membered heterocyclic ring which optionally contains additional heteroatoms selected from oxygen, S, SO, $SO_2$ or $NR^8$ where $R^8$ is hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkylsulfonyl or (1-6C)alkylcarbonyl;

provided that the quinazoline derivative is not:

4-[(3-chloro-4-fluorophenyl)amino]-6-[1-(tert-butyloxycarbonyl)-piperidin-4-yl-oxy]-7-methoxy-quinazoline;

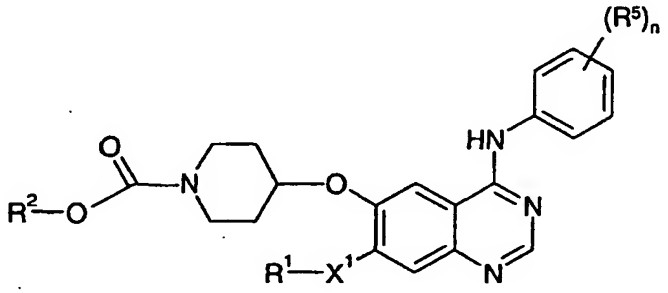
4-[(3-chloro-4-fluorophenyl)amino]-6-[1-(isopropyloxycarbonyl)-piperidin-4-yl-oxy]-7-methoxy-quinazoline;

4-[(3-ethynyl-phenyl)amino]-6-[1-(tert-butyloxycarbonyl)-piperidin-4-yl-oxy]-7-methoxy-quinazoline; or

6-{[(1-tert-butoxycarbonyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline;

or a pharmaceutically acceptable salt thereof.

According to another aspect of the invention there is provided a quinazoline derivative of the Formula I:



I

wherein n is 0, 1, 2 or 3,

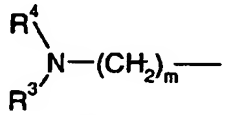
each $R^5$ is independently selected from halogeno, cyano, nitro, hydroxy, amino, carboxy, sulfamoyl, trifluoromethyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylsulfamoyl, and N,N-di-[(1-6C)alkyl]sulfamoyl, $C(O)NR^6R^7$ where $R^6$ and $R^7$ are independently selected from hydrogen, optionally substituted (1-6C)alkyl, optionally substituted (3-8C)cycloalkyl or optionally substituted aryl, or $R^6$ and $R^7$ together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring which may contain additional heteroatoms;

$X^1$ is a direct bond or O;

$R^1$ is selected from hydrogen and (1-6C)alkyl, wherein the (1-6C)alkyl group is optionally substituted by one or more substituents, which may be the same or different, selected from hydroxy and halogeno, and/or a substituent selected from amino, nitro, carboxy, cyano,

halogeno, (1-6C)alkoxy, hydroxy(1-6C)alkoxy, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, N-(1-6C)alkylcarbamoyl, N,N di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (1-6C)alkoxycarbonyl, sulfamoyl, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino;

$R^2$ is (1-6C)alkyl, (2-6C)alkenyl or (2-6C)alkynyl, any of which may be optionally substituted by fluoro, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, or a group of sub-formula (i)



(i)

wherein m is 1, 2 or 3;

$R^3$ and $R^4$ are independently selected from hydrogen or (1-6C)alkyl,

or $R^3$ and $R^4$ together with the nitrogen atom to which they are attached form a saturated 5 or 6 membered heterocyclic ring which optionally contains additional heteroatoms selected from oxygen, S, SO, $SO_2$ or $NR^8$ where $R^8$ is hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkylsulfonyl or (1-6C)alkylcarbonyl;

provided that the quinazoline derivative is not:

4-[(3-chloro-4-fluorophenyl)amino]-6-[1-(tert-butyloxycarbonyl)-piperidin-4-yl-oxy]-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-[1-(isopropyloxycarbonyl)-piperidin-4-yl-oxy]-7-methoxy-quinazoline;

4-[(3-ethynyl-phenyl)amino]-6-[1-(tert-butyloxycarbonyl)-piperidin-4-yl-oxy]-7-methoxy-quinazoline; or

6-{[(1-tert-butoxycarbonyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline;

or a pharmaceutically acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl, and (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain

version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy, cyclopropyloxy and cyclopentyloxy, (1-6C)alkylamino includes methylamino, ethylamino, cyclobutylamino and cyclohexylamino, and di-[(1-6Calkyl]amino includes dimethylamino, diethylamino, N-cyclobutyl-N-methylamino and N-cyclohexyl-N-ethylamino.

The term "aryl" refers to aromatic hydrocarbon rings such as phenyl or naphthyl. The terms "heterocyclic" or "heterocyclyl" include ring structures that may be mono- or bicyclic and contain from 3 to 15 atoms, at least one of which, and suitably from 1 to 4 of which, is a heteroatom such as oxygen, sulfur or nitrogen. Rings may be aromatic, non-aromatic or partially aromatic in the sense that one ring of a fused ring system may be aromatic and the other non-aromatic. Particular examples of such ring systems include furyl, benzofuranyl, tetrahydrofuryl, chromanyl, thienyl, benzothienyl, pyridyl, piperidinyl, quinolyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolyl, 1,2,3,4-tetrahydroisoquinolinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pyrrolyl, pyrrolidinyl, indolyl, indolinyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, morpholinyl, 4H-1,4-benzoxazinyl, 4H-1,4-benzothiazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, furazanyl, thiadiazolyl, tetrazolyl, dibenzofuranyl, dibenzothienyl oxiranyl, oxetanyl, azetidinyl, tetrahydropyranyl, oxepanyl, oxazepanyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, homopiperidinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, tetrahydrothienyl, tetrahydrothiopyranyl or thiomorpholinyl.

Particular examples of heterocyclic groups include tetrahydropyranyl, tetrahydrofuranyl or N-(1-6C)alkylpyrrolidine or N-(1-6C)alkylpiperidine.

Where rings include nitrogen atoms, these may carry a hydrogen atom or a substituent group such as an (1-6C)alkyl group if required to fulfil the bonding requirements of nitrogen, or they may be linked to the rest of the structure by way of the nitrogen atom. A nitrogen atom within a heterocyclyl group may be oxidized to give the corresponding N oxide.

Generally the compounds exhibit favourable physical properties such as a high solubility whilst retaining high antiproliferative activity. Furthermore, many of the compounds according to the present invention are inactive or only weakly active in a hERG assay.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetrically substituted carbon and/or sulfur atoms, and accordingly may exist in, and be isolated as enantiomerically pure, a mixture of diastereoisomers or as a racemate. The present invention includes in its definition any racemic, optically-active, enantiomerically pure, mixture of diastereoisomers, stereoisomeric form of the compound of Formula (I), or mixtures thereof, which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

The invention relates to all tautomeric forms of the compounds of the Formula I that possess antiproliferative activity.

It is also to be understood that certain compounds of the Formula I may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess antiproliferative activity.

It is also to be understood that certain compounds of the Formula I may exhibit polymorphism, and that the invention encompasses all such forms which possess antiproliferative activity.

Suitable values for the generic radicals referred to above include those set out below.

Suitable values for any of the $R^1$, $R^2$, $R^3$, $R^4$ or $R^5$ groups as defined hereinbefore or hereafter in this specification include:-

| | |
|---|---|
| for halogeno | fluoro, chloro, bromo and iodo; |
| for (1-6C)alkyl: | methyl, ethyl, propyl, isopropyl, tert-butyl, pentyl and hexyl; |
| for (1-4C)alkyl: | methyl, ethyl, propyl, isopropyl and tert-butyl; |
| for (1-6C)alkoxy: | methoxy, ethoxy, propoxy, isopropoxy and butoxy; |
| for (2-8C)alkenyl: | vinyl, isopropenyl, allyl and but-2-enyl; |
| for (2-8C)alkynyl: | ethynyl, 2-propynyl and but-2-ynyl; |
| for (2-6C)alkenyloxy: | vinyloxy and allyloxy; |
| for (2-6C)alkynyloxy: | ethynyloxy and 2-propynyloxy; |
| for (1-6C)alkylthio: | methylthio, ethylthio and propylthio; |

| | |
|---|---|
| for (1-6C)alkylsulfinyl: | methylsulfinyl and ethylsulfinyl; |
| for (1-6C)alkylsulfonyl: | methylsulfonyl and ethylsulfonyl; |
| for (1-6C)alkylamino: | methylamino, ethylamino, propylamino, isopropylamino and butylamino; |
| for di-[(1-6C)alkyl]amino: | dimethylamino, diethylamino, N-ethyl-N-methylamino and diisopropylamino; |
| for (1-6C)alkoxycarbonyl: | methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl; |
| for N-(1-6C)alkylcarbamoyl: | N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl and N-isopropylcarbamoyl; |
| for N,N-di-[(1-6C)alkyl]carbamoyl: | N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl; |
| for (2-6C)alkanoyl: | acetyl, propionyl and isobutyryl; |
| for (2-6C)alkanoyloxy: | acetoxy and propionyloxy; |
| for (2-6C)alkanoylamino: | acetamido and propionamido; |
| for N-(1-6C)alkyl-(2-6C)alkanoylamino: | N-methylacetamido and N-methylpropionamido; |
| for N-(1-6C)alkylsulfamoyl: | N-methylsulfamoyl, N-ethylsulfamoyl and N-isopropylsulfamoyl; |
| for N,N-di-[(1-6C)alkyl]sulfamoyl: | N,N-dimethylsulfamoyl and N-methyl-N-ethylsulfamoyl; |
| for (1-6C)alkanesulfonylamino: | methanesulfonylamino and ethanesulfonylamino; |
| for N-(1-6C)alkyl-(1-6C)alkanesulfonylamino: | N-methylmethanesulfonylamino and N-methylethanesulfonylamino; |
| for hydroxy-(1-6C)alkoxy: | hydroxymethoxy, 2-hydroxyethoxy, 1-hydroxyethoxy and 3-hydroxypropoxy. |

It is to be understood that when, $R^1$ is a group (1-6C)alkyl substituted by, for example amino to give for example a 2-aminoethyl group, it is the (1-6C)alkyl group that is attached to the group $X^1$ (or the quinazoline ring when $X^1$ is a direct bond).

When in this specification reference is made to a (1-4C)alkyl group it is to be understood that such groups refer to alkyl groups containing up to 4 carbon atoms. A skilled person will realise that representative examples of such groups are those listed above under (1-6C)alkyl that contain up to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl and tert-butyl. Similarly, reference to a (1-3C)alkyl group refers to alkyl groups containing

up to 3 carbon atoms such as methyl, ethyl, propyl and isopropyl. A similar convention is adopted for the other groups listed above such as (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl and (2-4C)alkanoyl.

In the compound of Formula I hydrogen atoms are present at the 2, 5 and 8 positions on the quinazoline ring.

A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulfuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular examples of n are 1, 2 or 3, suitably 2 or 3.

Suitably each $R^5$ is independently selected from halogeno, trifluoromethyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl or a group $C(O)NR^6R^7$ where $R^6$ and $R^7$ are as defined above.

In particular, each group $R^5$ is independently selected from halogeno, such as chloro or fluoro.

Particular substituents for groups $R^6$ and $R^7$ where these are other than hydrogen, include halogeno, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, sulfamoyl, trifluoromethyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkyl carbamoyl, N,N-di-[(1-6C)alkyl] carbamoyl, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (3-8C)cycloalkyl, aryl or heterocyclic groups.

Particular examples of aryl substituents for $R^6$ or $R^7$ include phenyl or naphthyl, particularly phenyl.

Particular examples of heterocyclic substituents for $R^6$ or $R^7$ include 5 or 6 membered heterocyclic rings such as furyl, tetrahydrofuryl, thienyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrrolidinyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, morpholinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, furazanyl, thiadiazolyl or tetrazolyl.

When $R^6$ and $R^7$ together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring, it is for example a 5 or 6 membered ring, which is saturated or unsaturated. Particular examples include piperidinyl, pyrrolidinyl, morpholinyl or thiomorpholino. Alternatively, $R^6$ and $R^7$ together form a (3-6C)alkenyl group.

Heterocyclic rings formed by $R^6$ and $R^7$ together with the nitrogen atom to which they are attached may be substituted by any of the groups mentioned above in relation to $R^6$ and $R^7$. In addition, these rings may be substituted by one or more (1-6C) alkyl groups, which may themselves be optionally substituted by one or more groups selected from halogeno, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, sulfamoyl, trifluoromethyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl] carbamoyl, N-(1-6C)alkylsulfamoyl, or N,N-di-[(1-6C)alkyl]sulfamoyl.

An exemplary group of substituents for $R^6$ or $R^7$ where they are other than hydrogen are cyano, hydroxy, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylamino, aryl such as phenyl or heterocyclic groups such as furyl, and additionally, where $R^6$ and $R^7$ together with the nitrogen atom to which they are attached form a ring, (1-6C) alkyl groups such as methyl.

Where n is 1, 2 or 3, one group $R^5$ is suitably at an ortho- position on the benzene ring.

Where n is 1, 2 or 3, one group $R^5$ is suitably at a meta- position on the benzene ring.

Thus, when n is 1, the group $R^5$ is suitably at an ortho- or a meta-position on the benzene ring,

In one aspect of the invention, when n is 2, the first $R^5$ group is suitably at a meta-position and the second $R^5$ group is suitably at an ortho- or para- position on the benzene ring, and thus the ring has substituents at 2- and 3- or 3- and 4- positions on the benzene ring.

In another aspect of the invention, when n is 2 or 3, the first $R^5$ group is suitably at an ortho- position, the second $R^5$ group is suitably at a meta- position and, optionally (when n is 3), the third $R^5$ group is suitably at a para- position on the benzene ring. Thus, when n is 2, the ring suitably has substituents at 2- and 3- positions on the benzene ring and when n is 3, the ring suitably has substituents at 2-, 3- and 4- positions on the benzene ring.

The applicants have surprisingly found that quinazoline derivatives having substituents (for example halogeno substituents) at 2- and 3- positions or at 2-, 3- and 4-positions on the benzene ring compared to quinazoline derivatives having substituents at 3-

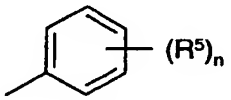
and 4- positions on the benzene ring produces a select group of compounds with enhanced activity in that the compounds have an increased potency against erbB2 and/or EGFR (particularly erbB2) receptor tyrosine kinases in cellular assays. It is believed that quinazoline derivatives having substituents (for example halogeno substituents) at 2- and 3- positions or at 2-, 3- and 4- positions on the benzene ring will also have an increased potency against both erbB2 and/or EGFR (particularly erbB2) receptor tyrosine kinases *in vivo*.

Suitably when n is 2 or 3, each $R^5$ group is the same or different halogeno atom, such as chloro or fluoro. Suitably, at least one $R^5$ group is fluoro, which at least one fluoro is suitably positioned at an ortho- (2-) position on the benzene ring.

Suitably when n is 2, each $R^5$ group is the same or different halogeno atom. In particular, one $R^5$ group is chloro, and this is preferably at a meta- (3-) position on the benzene ring to which it is attached, and the other $R^5$ group is fluoro which is preferably at an ortho- (2-) or a para- (4-) (preferably an ortho- (2-)) position on the benzene ring.

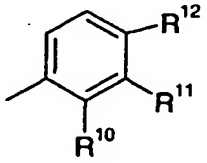
Suitably when n is 3, each $R^5$ group is the same or different halogeno atom. In particular, one $R^5$ group is chloro, and this is preferably at a meta- (3-) position on the benzene ring to which it is attached, and the other two $R^5$ groups are each fluoro, which are preferably at an ortho- (2-) and a para- (4-) position respectively on the benzene ring.

Thus particular examples of the group of sub-formula (ii):



(ii)

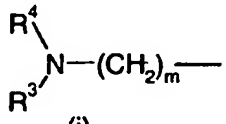
in Formula (I) are groups of sub-formula (iii):



(iii)

wherein (a) one of $R^{10}$ or $R^{12}$ is hydrogen and the other is halogeno, such as chloro or fluoro, and particularly fluoro, and $R^{11}$ is halogeno such as chloro or fluoro, and particularly chloro, or (b) $R^{10}$ is halogeno, such as chloro or fluoro, and particularly fluoro, $R^{11}$ is halogeno such as chloro or fluoro, and particularly chloro, and $R^{12}$ is hydrogen or halogeno, such as chloro or fluoro, and particularly fluoro, or (c) $R^{10}$ is fluoro, $R^{11}$ is chloro, and $R^{12}$ is hydrogen or fluoro. In particular, $R^{10}$, $R^{11}$ and $R^{12}$ are as defined in (b) and/or (c).

In one embodiment, when n is 2, each $R^5$ group is the same or different halogeno atom (such as fluoro and/or chloro) and the first $R^5$ group is at an ortho- position and the second $R^5$ group is at a meta- position on the benzene ring, then $R^2$ is not (optionally substituted) (1-6C)alkyl. In particular, $R^2$ is not (1-6C)alkyl optionally substituted by fluoro, (1-6C)alkoxy or a group of the sub-formula (i)



(i)

wherein m is 0 and $R^3$ and $R^4$ are independently selected from hydrogen or (1-4C)alkyl.

Suitably $X^1$ is oxygen.

In particular $R^1$ is selected from hydrogen, (1-6C)alkyl and (1-6C)alkoxy(1-6C)alkyl, wherein any (1-6C)alkyl group in $R^1$ optionally bears one or more (suitably 1 or 2) hydroxy or halogeno substituents. More particularly, $R^1$ is selected from (1-6C)alkyl, preferably from (1-4C)alkyl and even more preferably from (1-2C)alkyl. For example, $R^1$ may be methyl.

For instance, $R^1$-$X^1$- is selected from methoxy, ethoxy, isopropyloxy, cyclopropylmethoxy, 2-hydroxyethoxy, 2-fluoroethoxy, 2-methoxyethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy or 3-hydroxy-3-methylbutoxy.

In particular $R^1$-X- is selected from hydrogen, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkoxy. For instance, $R^1$-X- is selected from hydrogen, methoxy, ethoxy and 2-methoxyethoxy. A particular example of a group $R^1$-$X^1$- is methoxy.

Suitably $R^2$ is (1-6C)alkyl (particularly (1-3C)alkyl, more particularly (1-2C)alkyl) which is optionally substituted by a fluoro, (1-6C)alkoxy, (1-6C)alkylthio, (1-6)alkylsulfinyl (1-6C)alkylsulfonyl, or a group of sub-formula (i) as defined above. A particular example of a substituent for $R^2$ is a group of sub-formula (i) as defined above.

In particular $R^2$ is a (1-3C)alkyl group such as methyl or ethyl, which is optionally substituted by a group of sub-formula (i) as defined above. When $R^2$ contains a substituent of sub-formula (i), m is suitably 0, 1 or 2.

When $R^2$ contains a substituent of sub-formula (i), m is suitably 1 or 2, and preferably 2. In another aspect, m is particularly 0 or 1.

When $R^3$ and $R^4$ together with the nitrogen atom to which they are attached form a saturated 5 or 6 membered heterocyclic ring which optionally contains additional heteroatoms, this suitably contains additional heteroatoms selected from O and $NR^8$, where $R^8$ is as defined in relation to Formula I.

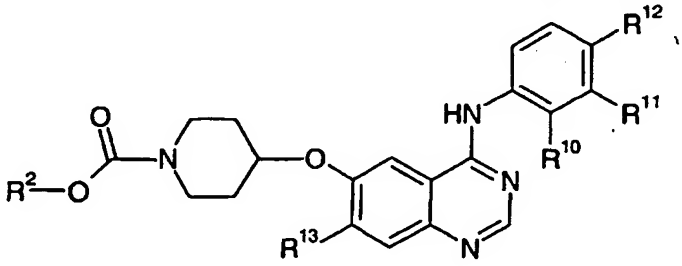
When $R^3$ and $R^4$ together with the nitrogen atom to which they are attached form a saturated 5 or 6 membered heterocyclic ring which optionally contains additional heteroatoms, this suitably comprises a pyrrolidine ring, a morpholine ring, a piperidine ring, or a piperazine ring which is optionally substituted on the available nitrogen atom by a group $R^8$ as defined above. Particular examples of $R^8$ groups include (1-3C) alkyl such as methyl; (1-3C)alkylsulfonyl such as methyl sulfonyl; (1-3C)alkylcarbonyl, such as acetyl; or (2-4C)alkenyl such allyl; or (2-4C)alkynyl such as propargyl. In particular $R^8$ is a (1-3C)alkyl group such as methyl.

Alternatively, the groups $R^3$ and $R^4$ may suitably be independently selected from (1-6C)alkyl, particularly from (1-3C)alkyl, such as methyl and ethyl. For example, each of the groups $R^3$ and $R^4$ may suitably be (1-3C)alkyl, such as, in one aspect, each of the groups $R^3$ and $R^4$ may be ethyl.

Particular examples of groups $R^2$ include methyl, 2-(pyrrolidin-1-yl)ethyl, 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, 2-(piperidinyl)ethyl, 2-(morpholin-4-yl)ethyl or 2-(4-methylpiperazin-1-yl)ethyl. More particularly, examples of groups $R^2$ include methyl, 2-(pyrrolidin-1-yl)ethyl, 2-(diethylamino)ethyl, 2-(piperidin-1-yl)ethyl, 2-(morpholin-4-yl)ethyl or 2-(4-methylpiperazin-1-yl)ethyl.

In a particular embodiment, $R^2$ is methyl. In an alternative embodiment, $R^2$ is selected from 2-(piperidin-1-yl)ethyl, 2-(4-methylpiperazin-1-yl)ethyl and 2-(pyrrolidin-1-yl)ethyl, particularly $R^2$ is 2-(pyrrolidin-1-yl)ethyl. In another alternative embodiment, $R^2$ is selected from 2-(dimethylamino)ethyl and 2-(diethylamino)ethyl. In another alternative embodiment, $R^2$ is 2-(morpholin-4-yl)ethyl.

Particular examples of the compounds of Formula I are compounds of Formula IA:



IA

where $R^2$ is as defined above in relation to Formula I, $R^{10}$, $R^{11}$ and $R^{12}$ are as defined above in relation to sub-formula (iii), and $R^{13}$ is selected from hydrogen, methoxy, ethoxy and 2-methoxyethoxy, and especially methoxy;

For the avoidance of any doubt, when the compounds of Formula I are defined as compounds of Formula IA, the quinazoline derinvative is not:

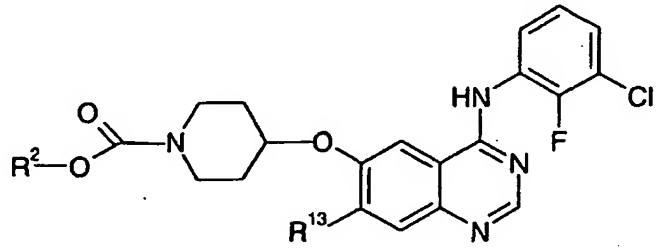
4-[(3-chloro-4-fluorophenyl)amino]-6-[1-(tert-butyloxycarbonyl)-piperidin-4-yl-oxy]-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-[1-(isopropyloxycarbonyl)-piperidin-4-yl-oxy]-7-methoxy-quinazoline; or

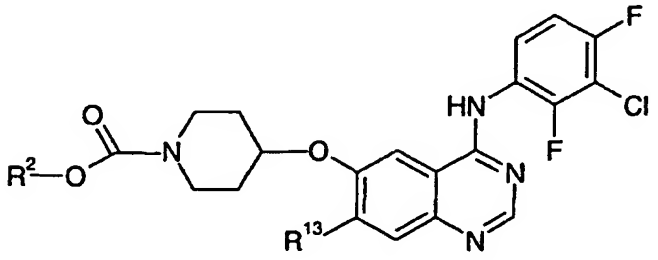
6-{[(1-tert-butoxycarbonyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline;

or a pharmaceutically acceptable salt thereof.

Other particular examples of the compounds of Formula I are compounds of the Formulae IB and/or IC:



IB

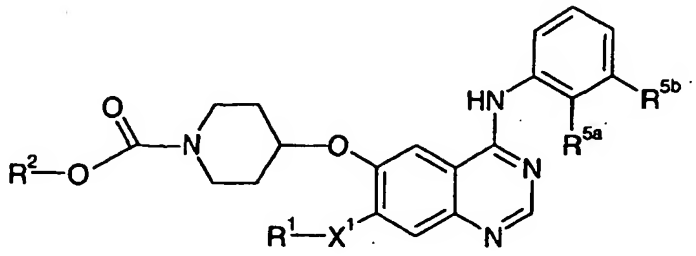


IC

where $R^2$ is as defined above in relation to Formula I and $R^{13}$ is selected from hydrogen, methoxy, ethoxy and 2-methoxyethoxy, and especially methoxy.

For the avoidance of any doubt, when the compounds of Formula I are defined as compounds of Formula IB, the quinazoline derivative is not 6-{[(1-tert-butoxycarbonyl) piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline, or a pharmaceutically acceptable salt thereof.

Other particular examples of the compounds of Formula I are compounds of the Formula ID:



ID

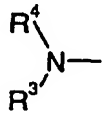
wherein:

$R^{5a}$ and $R^{5b}$ are independently selected from halogeno (for example fluoro and/or chloro);

$X^1$ is a direct bond or O;

$R^1$ is selected from hydrogen and (1-6C)alkyl, wherein the (1-6C)alkyl group is optionally substituted by one or more substituents, which may be the same or different, selected from hydroxy and halogeno, and/or a substituent selected from amino, nitro, carboxy, cyano, halogeno, (1-6C)alkoxy, hydroxy(1-6C)alkoxy, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, N-(1-6C)alkylcarbamoyl, N,N di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (1-6C)alkoxycarbonyl, sulfamoyl, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino;

$R^2$ is (1-6C)alkyl, wherein the (1-6C)alkyl group is optionally substituted by fluoro, (1-6C)alkoxy, or a group of sub-formula (iv)



(iv)

wherein $R^3$ and $R^4$ are independently selected from hydrogen or (1-4C)alkyl, or $R^3$ and $R^4$ together with the nitrogen atom to which they are attached form a saturated 5 or 6 membered heterocyclic ring which optionally contains additional heteroatoms selected from oxygen, S, SO, $SO_2$ or $NR^8$ where $R^8$ is hydrogen, (1-4C)alkyl or (1-4C)alkylsulfonyl; or a pharmaceutically acceptable salt thereof.

For the avoidance of any doubt, when the compounds of Formula I are defined as compounds of Formula ID, the quinazoline derivative is not 6-{[(1-tert-butoxycarbonyl) piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline, or a pharmaceutically acceptable salt thereof.

In the compounds of the Formula ID, the group $R^2$ is suitably (1-6C)alkyl, particularly unsubstituted (1-6C)alkyl. For example, the group $R^2$ may be methyl or ethyl, particularly methyl.

In the compounds of the Formula ID, $X^1$ is suitably oxygen. $R^1$ is suitably selected from hydrogen and (1-6C)alkyl, wherein any (1-6C)alkyl group in $R^1$ optionally bears one or more (suitably 1 or 2) hydroxy or halogeno substituents. More particularly, $R^1$ is selected from (1-6C)alkyl, preferably from (1-4C)alkyl and even more preferably from (1-2C)alkyl. For example, $R^1$ may be methyl. A particular example of a group $R^1$-$X^1$ in the compounds of Formula ID is methoxy.

It would be clear to a person skilled in the art that particular novel compounds of the invention include those compounds of the Formula I (including IA, IB, IC and ID) in which, unless otherwise stated, each of $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $X^1$, m and n has any of the meanings as hereinbefore defined.

Examples of compounds of Formula I include, for example, one or more of:

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(methoxycarbonyl)piperidin-4-yl]oxy} quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(pyrrolidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-2-(N, N-dimethylamino)ethoxycarbonyl) piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-4-fluoroanilino)-7-methoxy-6-{[1-{2-(pyrrolidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloroanilino)-7-methoxy-6-{[1-{2-(pyrrolidin-1-yl)ethoxycarbonyl}piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-(methoxycarbonyl)piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-{2-(pyrrolidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-{2-(piperidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(piperidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)- 6-{[1-{2-(diethylamino)ethoxycarbonyl}piperidin-4-yl]oxy}-7-methoxyquinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(morpholin-4-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline; and

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(4-methylpiperidin-1-yl) ethoxycarbonyl}piperidin-4-yl]oxy}quinazoline;

or a pharmaceutically acceptable salt thereof.

Preferred examples of compounds of Formula I include, for example, one or more of:

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(methoxycarbonyl)piperidin-4-yl]oxy} quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(pyrrolidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-(methoxycarbonyl)piperidin-4-yl] oxy}quinazoline;

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-{2-(pyrrolidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-{2-(piperidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(piperidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)- 6-{[1-{2-(diethylamino)ethoxycarbonyl}piperidin-4-yl] oxy}-7-methoxyquinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(morpholin-4-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline; and

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(4-methylpiperidin-1-yl) ethoxycarbonyl}piperidin-4-yl]oxy}quinazoline;

or a pharmaceutically acceptable salt thereof.

A particular group of examples of quinazoline derivatives of the Formula IA includes one or more of:

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(methoxycarbonyl)piperidin-4-yl]oxy} quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(pyrrolidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-2-(N, N-dimethylamino)ethoxycarbonyl) piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-4-fluoroanilino)-7-methoxy-6-{[1-{2-(pyrrolidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-(methoxycarbonyl)piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-{2-(pyrrolidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-{2-(piperidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(piperidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)- 6-{[1-{2-(diethylamino)ethoxycarbonyl}piperidin-4-yl]oxy}-7-methoxyquinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(morpholin-4-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline; and

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(4-methylpiperidin-1-yl) ethoxycarbonyl}piperidin-4-yl]oxy}quinazoline;

or a pharmaceutically acceptable salt thereof.

A particular group of examples of quinazoline derivatives of the Formula IB includes one or more of:

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(methoxycarbonyl)piperidin-4-yl]oxy} quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(pyrrolidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-2-(N, N-dimethylamino)ethoxycarbonyl) piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(piperidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)- 6-{[1-{2-(diethylamino)ethoxycarbonyl}piperidin-4-yl]oxy}-7-methoxyquinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(morpholin-4-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline; and

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(4-methylpiperidin-1-yl) ethoxycarbonyl}piperidin-4-yl]oxy}quinazoline;

or a pharmaceutically acceptable salt thereof.

A particular group of examples of quinazoline derivatives of the Formula IC includes one or more of:

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-(methoxycarbonyl)piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-{2-(pyrrolidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline; and

4-(3-Chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-{2-(piperidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

or a pharmaceutically acceptable salt thereof.

A particular example of a quinazoline derivative of the Formula ID is:

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(methoxycarbonyl)piperidin-4-yl]oxy} quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(pyrrolidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-2-(N, N-dimethylamino)ethoxycarbonyl) piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(piperidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline;

4-(3-Chloro-2-fluoroanilino)- 6-{[1-{2-(diethylamino)ethoxycarbonyl}piperidin-4-yl]oxy}-7-methoxyquinazoline;

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(morpholin-4-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline; and

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(4-methylpiperidin-1-yl) ethoxycarbonyl}piperidin-4-yl]oxy}quinazoline;

or a pharmaceutically acceptable salt thereof.

Preferred compounds of Formula I are, for example, one or more of:

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(methoxycarbonyl)piperidin-4-yl]oxy} quinazoline; and

4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-{2-(pyrrolidin-1-yl)ethoxycarbonyl} piperidin-4-yl]oxy}quinazoline,

or a pharmaceutically acceptable salt thereof.

**Synthesis of Quinazoline Derivatives of the Formula I**

A further aspect the present invention provides a process for preparing a quinazoline derivative of Formula I or a pharmaceutically-acceptable salt thereof. It will be appreciated that during certain of the following processes certain substituents may require protection to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed.

For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group

for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium, sodium hydroxide or ammonia. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

Resins may also be used as a protecting group.

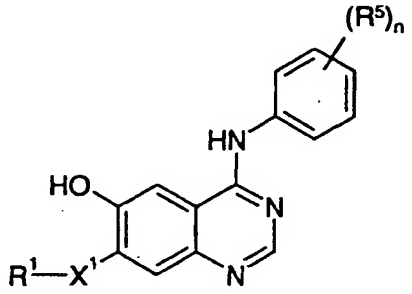
The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

A quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt thereof, are provided as a further feature of the invention and are illustrated by the following representative examples. Necessary starting materials may be obtained by standard procedures of organic chemistry (see, for example, Advanced Organic Chemistry (Wiley-Interscience), Jerry March). The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively, necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist. Information on the preparation of necessary starting materials or related compounds (which may be adapted to form necessary starting materials) may also be found in the following Patent and Application Publications, the contents of the relevant process sections of which are hereby incorporated herein by reference: WO94/27965, WO 95/03283, WO 96/33977, WO

96/33978, WO 96/33979, WO 96/33980, WO 96/33981, WO 97/30034, WO 97/38994, WO01/66099, US 5,252,586, EP 520 722, EP 566 226, EP 602 851 and EP 635 507.

The present invention also provides that quinazoline derivatives of the Formula I, or pharmaceutically acceptable salts thereof, can be prepared by a process (a) to (k) as follows (wherein the variables are as defined above unless otherwise stated):

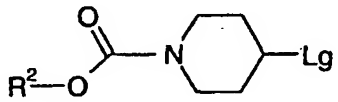
**Process (a)** By reacting a compound of the Formula II:



II

wherein $R^1$, $X^1$, $R^5$ and n have any of the meanings defined hereinbefore except that any functional group is protected if necessary,

with a compound of the Formula III:



III

wherein $R^2$ has any of the meanings defined hereinbefore except that any functional group is protected if necessary and Lg is a displaceable group, wherein the reaction is conveniently performed in the presence of a suitable base,

and whereafter any protecting group that is present is removed by conventional means.

A convenient displaceable group Lg is, for example, a halogeno, alkanesulfonyloxy or arylsulfonyloxy group, for example a chloro, bromo, methanesulfonyloxy, 4-nitrobenzenesulfonyloxy or toluene-4-sulfonyloxy group (suitably a methanesulfonyloxy, 4-nitrobenzenesulfonyloxy or toluene-4-sulfonyloxy group).

The reaction is advantageously carried out in the presence of base. A suitable base is, for example, an organic amine base such as, for example, di-isopropylethylamine, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or for example, an alkali metal or alkaline earth metal

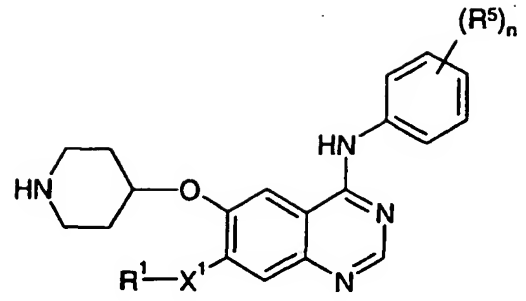
carbonate or hydroxide, for example sodium carbonate, potassium carbonate, cesium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively such a base is, for example, an alkali metal hydride, for example sodium hydride, an alkali metal or alkaline earth metal amide, for example sodium amide or sodium bis(trimethylsilyl)amide, or a sufficiently basic alkali metal halide, for example cesium fluoride or sodium iodide. The reaction is suitably effected in the presence of an inert solvent or diluent, for example an alkanol or ester such as methanol, ethanol, 2-propanol or ethyl acetate, a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene, or (suitably) a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently effected at a temperature in the range, for example, 10 to 150°C (or the boiling point of the solvent), suitably in the range 20 to 90°C.

A particularly suitable base is cesium fluoride. This reaction is suitably performed in an inert dipolar aprotic solvent such as N,N-dimethylacetamide or N,N-dimethylformamide. The reaction is suitably carried out at a temperature of from 25 to 85°C.

**Process (b)** By modifying a substituent in or introducing a substituent into another quinazoline derivative of Formula I or a pharmaceutically acceptable salt thereof, as hereinbefore defined except that any functional group is protected if necessary, and whereafter any protecting group that is present is removed by conventional means.

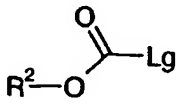
Methods for converting substituents into other substituents are known in the art. For example an alkylthio group may be oxidised to an alkylsulfinyl or alkylsulfonyl group, a cyano group reduced to an amino group, a nitro group reduced to an amino group, a hydroxy group alkylated to a methoxy group, a bromo group converted to an alkylthio group, an amino group may be acylated to give an alkanoylamino group (for example by reaction with a suitable acid chloride or acid anhydride) or an alkanoyloxy group may be hydrolysed to a hydroxy group (for example an acetyloxyacetyl group may be converted to a hydroxyacetyl group). Conveniently, one $R^1$ group may be converted into another $R^1$ group as a final step in the preparation of a compound of the Formula I.

**Process (c)** By reacting a compound of Formula IV:



IV

where $R^1$, $X^1$, $R^5$ and n are as defined in relation to Formula I, with a compound of Formula V:



V

wherein $R^2$ is as defined above, and Lg is a displaceable group (for example halogeno such as chloro or bromo, or 1-imidazolyl). The reactions described above are conveniently performed in the presence of a suitable base (such as those described above in process (a), for example potassium carbonate or di-isopropylethylamine) and conveniently in the presence of an inert solvent or diluent (for example the inert solvents and diluents described in process (a) such as acetonitrile, N,N-dimethylacetamide, methanol, ethanol or methylene chloride).

**Process (d)** By removal of a protecting group from a quinazoline derivative of Formula I, or a pharmaceutically acceptable salt thereof.

Suitable methods for removal of protecting groups are well known and are discussed herein. For example for the production of those compounds of the Formula I wherein $R^1$ contains a primary or secondary amino group, the cleavage of the corresponding compound of Formula I wherein $R^1$ contains a protected primary or secondary amino group.

Suitable protecting groups for an amino group are, for example, any of the protecting groups disclosed hereinbefore for an amino group. Suitable methods for the cleavage of such amino protecting groups are also disclosed hereinbefore. In particular, a suitable protecting group is a lower alkoxycarbonyl group such as a tert-butoxycarbonyl group which may be cleaved under conventional reaction conditions such as under acid-catalysed hydrolysis, for example in the presence of trifluoroacetic acid.

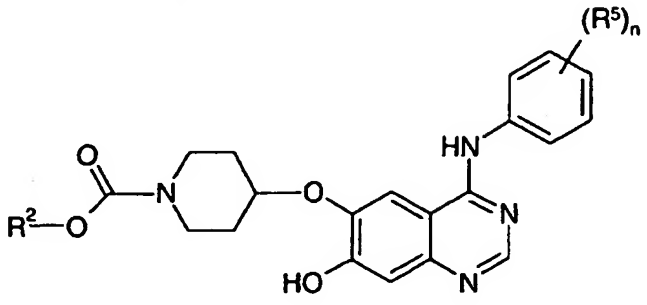
**Process (e)** By reacting a compound of the Formula II as hereinbefore defined with a compound of the Formula III as defined hereinbefore except Lg is OH under Mitsunobu conditions, and whereafter any protecting group that is present is removed by conventional means.

Suitable Mitsunobu conditions include, for example, reaction in the presence of a suitable tertiary phosphine and a di-alkylazodicarboxylate in an organic solvent such as THF, or suitably dichloromethane and in the temperature range 0°C - 60°C, but suitably at ambient temperature. A suitable tertiary phosphine includes for example tri-n-butylphosphine or suitably tri-phenylphosphine. A suitable di-alkylazodicarboxylate includes for example diethyl azodicarboxylate (DEAD) or suitably di-tert-butyl azodicarboxylate. Details of Mitsunobu reactions are contained in Tet. Letts., 31, 699, (1990); The Mitsunobu Reaction, D.L.Hughes, Organic Reactions, 1992, Vol.42, 335-656 and Progress in the Mitsunobu Reaction, D.L.Hughes, Organic Preparations and Procedures International, 1996, Vol.28, 127-164.

**Process (f)** For the preparation of those compounds of the Formula I wherein $R^1$-$X^1$ is a hydroxy group by the cleavage of a quinazoline derivative of the Formula I wherein $R^1$-$X^1$ is a (1-6C)alkoxy group.

The cleavage reaction may conveniently be carried out by any of the many procedures known for such a transformation. The cleavage reaction of a compound of the Formula I wherein $R^1$ is a (1-6C)alkoxy group may be carried out, for example, by treatment of the quinazoline derivative with an alkali metal (1-6C)alkylsulfide such as sodium ethanethiolate or, for example, by treatment with an alkali metal diarylphosphide such as lithium diphenylphosphide. Alternatively the cleavage reaction may conveniently be carried out, for example, by treatment of the quinazoline derivative with a boron or aluminium trihalide such as boron tribromide, or by reaction with an organic or inorganic acid, for example trifluoroacetic acid. Such reactions are suitably carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore. A preferred cleavage reaction is the treatment of a quinazoline derivative of the Formula I with pyridine hydrochloride. The cleavage reactions are suitably carried out at a temperature in the range, for example, from 10 to 200°C. In some cases this may be achieved at temperatures, for example from 25 to 80°C, but in other cases, for instance using a pyridine hydrochloride deprotection, melting typically at 160-200°C is suitable.

**Process (g)** For the preparation of those compounds of the Formula I wherein $X^1$ is O, by the reaction of a compound of the Formula VI:



VI

wherein $R^2$, $R^5$ and n have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the formula $R^1$-Lg, wherein $R^1$ has any of the meanings defined hereinbefore, except that any functional group is protected if necessary and Lg is a displaceable group, wherein the reaction is conveniently performed in the presence of a suitable base;

and whereafter any protecting group that is present is removed by conventional means.

Suitable displaceable groups, Lg, are as hereinbefore defined for process (a), for example chloro or bromo. The reaction is suitably performed in the presence of a suitable base. Suitable solvents, diluents and bases include, for example those hereinbefore described in relation to process (a) above. Alternatively, Lg may be OH whereupon the reaction is carried out under Mitsunobu conditions, as described in process (e) above.

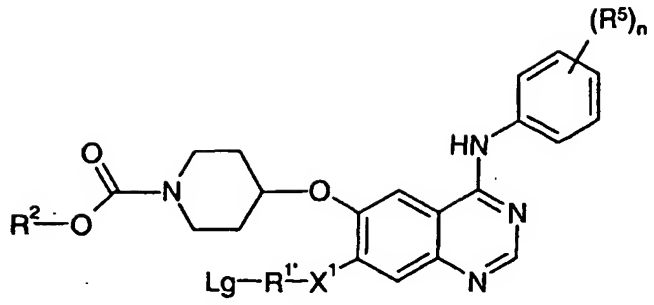
**Process (h)** For the preparation of those compounds of the Formula I wherein $R^1$ contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the alkylation, conveniently in the presence of a suitable base as defined hereinbefore for process (a), of a quinazoline derivative of the Formula I wherein or $R^1$ contains a hydroxy group or a primary or secondary amino group as appropriate.

A suitable alkylating agent is, for example, any agent known in the art for the alkylation of hydroxy to alkoxy or substituted alkoxy, or for the alkylation of amino to alkylamino or substituted alkylamino, for example an alkyl or substituted alkyl halide, for example a (1-6C)alkyl chloride, bromide or iodide or a substituted (1-6C)alkyl chloride, bromide or iodide, conveniently in the presence of a suitable base as defined hereinbefore, in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 140°C, conveniently at or near ambient temperature. An analogous procedure

may be used to introduce optionally substituted (2-6C)alkanoyloxy, (2-6C)alkanoylamino and (1-6C)alkanesulfonylamino groups into $R^1$.

Conveniently for the production of those compounds of the Formula I wherein $R^1$ contains a (1-6C)alkylamino or substituted (1-6C)alkylamino group, a reductive amination reaction may be employed using formaldehyde or a (2-6C)alkanolaldehyde (for example acetaldehyde or propionaldehyde). For example, for the production of those compounds of the Formula I wherein $R^1$ contains an N-methyl group, the corresponding compound containing a N-H group may be reacted with formaldehyde in the presence of a suitable reducing agent. A suitable reducing agent is, for example, a hydride reducing agent, for example formic acid, an alkali metal aluminium hydride such as lithium aluminium hydride, or, suitably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and sodium triacetoxyborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran and diethyl ether for the more powerful reducing agents such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride and sodium cyanoborohydride. When the reducing agent is formic acid the reaction is conveniently carried out using an aqueous solution of the formic acid. The reaction is performed at a temperature in the range, for example, 10 to 100°C, such as 70 to 90°C or, conveniently, at or near ambient temperature. Conveniently, when the reducing agent is formic acid, protecting groups such as tert-butoxycarbonyl on the NH group to be alkylated (for example present from the synthesis of the starting material) may be removed in-situ during the reaction.

**Process (i)** For the preparation of those compounds of the Formula I wherein $R^1$ is substituted by a group T, wherein T is selected from (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoylamino, (1-6C)alkylthio, (1-6C)alkylsulfinyl and (1-6C)alkylsulfonyl, the reaction of a compound of the Formula VII:



VII

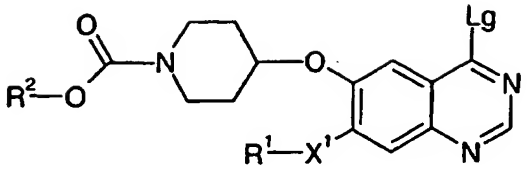
wherein $R^2$, $R^5$, $X^1$, n and m have any of the meanings defined hereinbefore except that any functional group is protected if necessary, $R^{1'}$ is a group $R^1$ as defined herein except that any T groups are replaced with Lg, and Lg is a displaceable group (for example chloro or bromo or aryl/(1-6C)alkyl sulfonates such as mesylate) with a compound of the formula TH, wherein T is as defined above except that any functional group is protected if necessary;

and whereafter any protecting group that is present is removed by conventional means.

The reaction is conveniently carried out in the presence of a suitable base. The reaction may conveniently be performed in a suitable inert solvent or diluent. Suitable bases, solvents and diluents are for example those described under process (a). The reaction is suitably performed at a temperature of for example, from 10 to 150°C, for example 30 to 60°C.

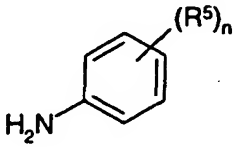
It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group.

**Process (j)** By reacting a compound of the Formula VIII:



VIII

wherein $R^1$, $R^2$, $X^1$, and m have any of the meanings defined hereinbefore except that any functional group is protected if necessary and Lg is a displaceable group as hereinbefore defined, with an aniline of the Formula IX:



IX

wherein $R^5$ and n have any of the meanings defined hereinbefore except that any functional group is protected if necessary, and wherein the reaction is conveniently performed in the presence of a suitable acid,

and whereafter any protecting group that is present is removed by conventional means.

Suitable displaceable groups represented by Lg are as hereinbefore defined, in particular halogeno such as chloro.

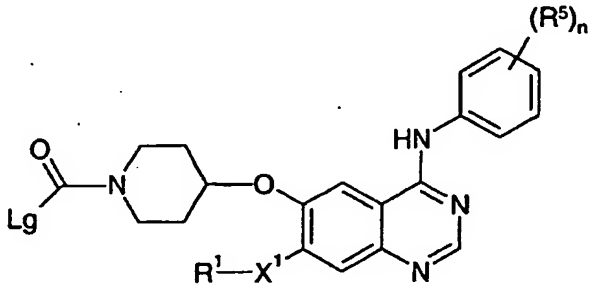
The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one acetonitrile or dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 250°C, conveniently in the range 40 to 120°C or where a solvent or diluent is used at the reflux temperature. Conveniently, the compound of Formula VIII may be reacted with a compound of the Formula IX in the presence of a protic solvent such as isopropanol, conveniently in the presence of an acid, for example a catalytic amount of an acid, under the conditions described above. Suitable acids include hydrogen chloride gas in diethyl ether or dioxane, and hydrochloric acid, for example a 4M solution of hydrogen chloride in dioxane. Alternatively, this reaction may be

conveniently carried out in an aprotic solvent, such as dioxane or a dipolar aprotic solvent such as N,N-dimethylacetamide or acetonitrile in the presence of an acid, for example hydrogen chloride gas in diethyl ether or dioxane, or hydrochloric acid.

The compound of the Formula VIII, wherein Lg is halogeno, may be reacted with a compound of the Formula IX in the absence of an acid. In this reaction displacement of the halogeno leaving group Lg results in the formation of the acid HLg in-situ and auto-catalysis of the reaction. Conveniently the reaction is carried out in a suitable inert organic solvent, for example isopropanol, dioxane or N,N-dimethylacetamide. Suitable conditions for this reaction are as described above.

Alternatively, the compound of Formula VIII may be reacted with a compound of the Formula IX in the presence of a suitable base. Suitable bases for this reaction are as hereinbefore defined under process (a). For example, suitable bases are alkaline earth metal amides, such as sodium bis(trimethylsilyl)amide. This reaction is conveniently performed in an inert solvent or diluent, for example those mentioned above in relation to this process (j);

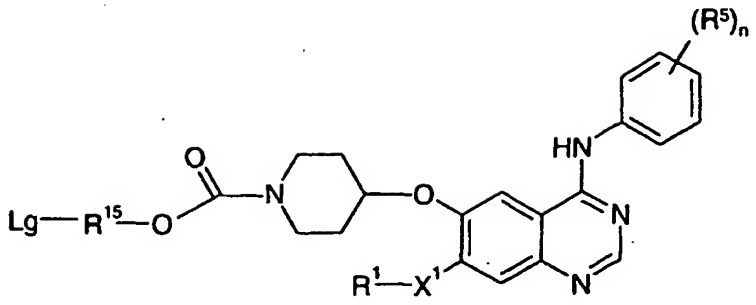
**Process (k)** By reacting a compound of Formula X:



X

where $R^5$, $X^1$, $R^1$ and n are as defined above, and where Lg is a leaving group, such as halogeno, especially chloro, or 1-imidazolyl, with an alcohol of formula $R^2$-OH, where $R^2$ is as defined above. The reaction is suitably affected in aprotic solvent such as DCM in the presence of a base such as tertiary amine/pyridine. Suitable temperatures will be apparent to a skilled chemist.

**Process (l)** for compounds where $R^2$ includes a group of sub-formula (i), reacting a compound of the Formula XI:



XI

where $R^1$, $X^1$, $R^5$, and n are as defined hereinbefore, $R^{15}$ is a (1-6C)alkylene group, and Lg is a leaving group, with a compound of formula $R^3R^4NH$ where $R^3$ and $R^4$ are as defined in relation to sub-formula (i) above. Suitable leaving groups Lg in this case include halogeno such as chloro, or an alkyl/aryl sulfonate such as mesylate). The reaction is suitably effected in the presence of an iodide source such as potassium iodide or tetrabutyl ammonium iodide in an organic solvent such a dimethylacetamide, N-methyl pyrrolidone or dimethylformamide. Suitably, an excess of the amine $R^3R^4NH$ is used. This may be useful, for example when Lg is chloro, to quench the hydrogen chloride that is formed during the course of the reaction. Elevated temperatures, for example of from 50-120°C, for example at about 80°C, are suitably employed.

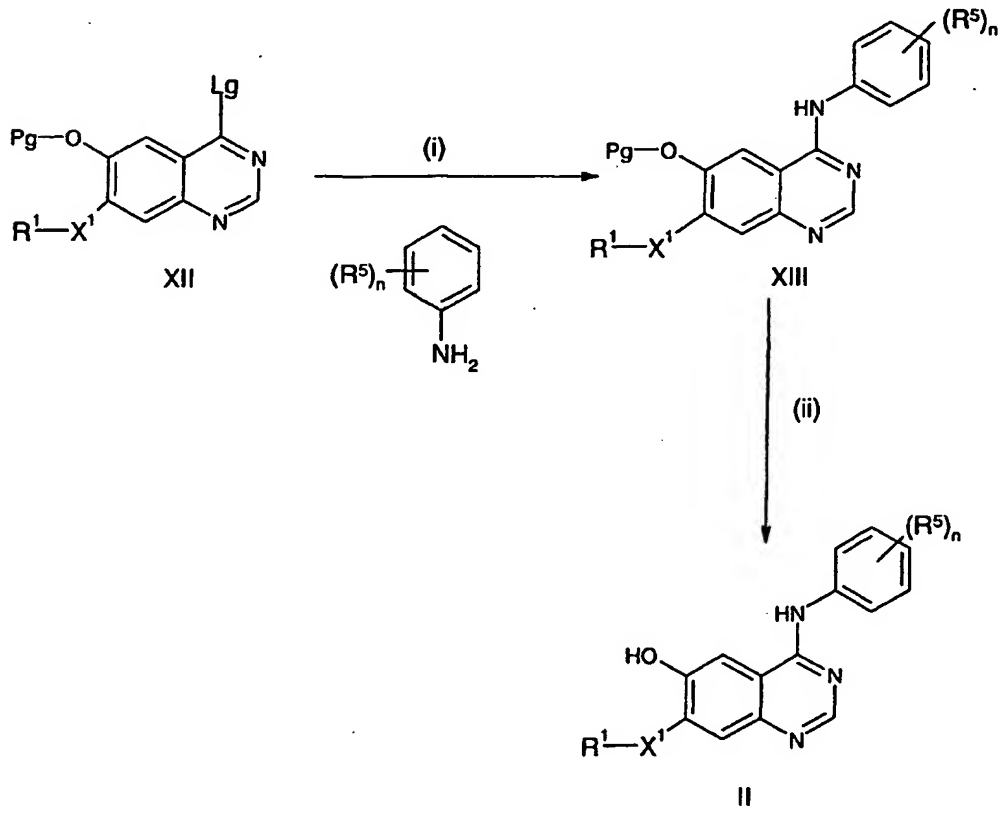
Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

When a pharmaceutically-acceptable salt of a quinazoline derivative of the Formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinazoline derivative with a suitable acid using a conventional procedure. To facilitate isolation of the compound during preparation, the compound may be prepared in the form of a salt that is not a pharmaceutically acceptable salt. The resulting salt can then be modified by conventional techniques to give a pharmaceutically acceptable salt of the compound. Such techniques include, for example ion exchange techniques or re-precipitation of the compound in the presence of a pharmaceutically acceptable counter ion. For example re-precipitation in the presence of a suitable acid such as HCl to give a hydrochloride acid addition salt.

In the section above the expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Preparation of Starting Materials

Compounds of Formula II are commercially available or may be prepared using conventional techniques or analogous processes to those described in the prior art. In particular those patents and applications listed hereinbefore, such as WO96/15118, WO 01/66099 and EP 566 226. For example, the compounds of Formula II may be prepared in accordance with Reaction Scheme 1:




*Reaction Scheme 1*

wherein $R^1$, $X^1$, $R^5$, Lg and n are as hereinbefore defined and Pg is a hydroxy protecting group.

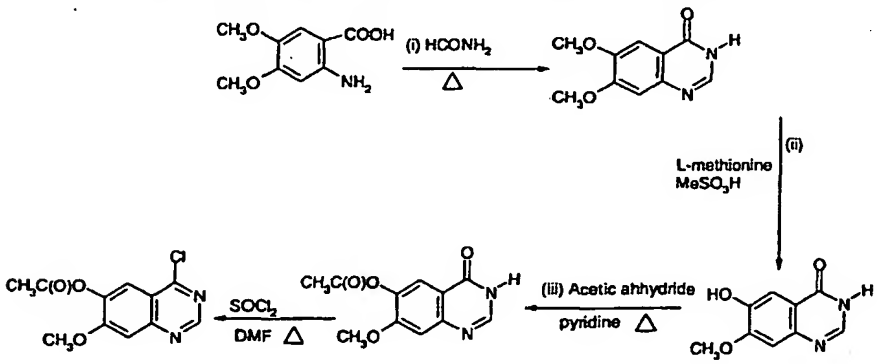
(i) Reaction suitably in an inert protic solvent (such as an alkanol for example iso-propanol), an aprotic solvent (such as dioxane) or a dipolar aprotic solvent (such as N,N-dimethylacetamide) in the presence of an acid, for example hydrogen chloride gas in diethyl

ether or dioxane, or hydrochloric acid, under analogous conditions to those described above under process (i).

Alternatively the reaction may be carried out in one of the above inert solvents conveniently in the presence of a base, for example potassium carbonate. The above reactions are conveniently carried out at a temperature in the range, for example, 0 to 150°C, suitably at or near the reflux temperature of the reaction solvent.

(ii) Cleavage of Pg may be performed under standard conditions for such reactions. For example when Pg is an alkanoyl group such as acetyl, it may be cleaved by heating in the presence of a methanolic ammonia solution.

Compounds of Formula XII are known or can be prepared using known processes for the preparation of analogous compounds. If not commercially available, compounds of the Formula XII may be prepared by procedures which are selected from standard chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the procedures described in the Examples. For example, standard chemical techniques are as described in Houben Weyl. By way of example the compound of the Formula XII in which $R^1$-$X^1$- is methoxy, Lg is chloro and Pg is acetyl may be prepared using the process illustrated in Reaction Scheme 2:




*Reaction Scheme 2*

Reaction Scheme 2 may be generalised by the skilled man to apply to compounds within the present specification which are not specifically illustrated (for example to introduce a substituent other than methoxy at the 7-position in the quinazoline ring).

Compounds of the Formula III are commercially available or may be prepared using standard techniques, for example as illustrated in US 5,252,586 and WO 94/27965.

Compounds of the Formula IV may be prepared by reaction of a compound of Formula II with a compound of XVa or XVb: